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09/477,082	12/30/1999	VINCENT J. KIDD	2427/IE988-U	8684

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EXAMINER

HOLLERAN, ANNE L

ART UNIT PAPER NUMBER

1642

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

## Application No.

09/477,082

## Applicant(s)

KIDD ET AL.

## Examiner

Anne Holleran

## Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 06 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 11,12,16,29,51 and 56-63 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 56,57 and 60-62 is/are allowed.
- 6) ☒ Claim(s) 11,12,16,29,51,58,59 and 63 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### DETAILED ACTION

1. The amendment filed July 6, 2004 is acknowledged.

Claims 11, 12, 16, 29, 51 and 56-63 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Claim Rejections Withdrawn:***

3. The rejection of claims 2, 3, 48-50, and 54 under 35 U.S.C. 102(b) as being anticipated by Dixit (WO 97/46662; published 11 Dec. 1997) is withdrawn in view of the amendment canceling the claims.

4. The rejection of claims 48, 54, 2, 3, 49, 50, 63, 51, 11-14, 64, and 65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

5. The rejection of claims 48, 54, 2, 3, 49, 50, 63, 51, 11, 12, 15, 16, 13, 14, 64 and 65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment.

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6. The rejection of claims 48, 54, 56, 60, 61, 63, 51, 11, 12, and 15 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detection of CASP8 genomic DNA methylation wherein the methylation is detected by methylation polymerase chain reaction (PCR) assay, does not reasonably provide enablement for any and all methods of detection of DNA methylation is withdrawn in view of applicants' persuasive arguments that more than one method of detection of DNA methylation were well-known to those of skill in the art at the time of the invention.

7. The rejection of claims 48, 2 and 3 under 35 U.S.C. 103(a) as being unpatentable over Mandruzatto (Mandrizzato, S. et al. J. Exp. Med., 186(5): 785-793, 1997, Aug.) is withdrawn in view of the cancellation of the claims.

8. The rejection of claims 48, 54, 2 and 3 under 35 U.S.C. 103(a) as being unpatentable over Scaffidi (supra) in view of Mandruzatto (Mandrizzato, S. et al., J. Exp. Med., 186(5): 785-793, 1997, Aug.; cited in the IDS) is withdrawn in view of the cancellation of the claims.

***Claim Rejections Maintained:***

9. The rejection of claims 51, 63, 11, 12, and 16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of prognosis of neuroblastoma, comprising the detection of methylation of CASP8 gene, does not reasonably provide enablement for methods of diagnosis or for methods of prognosis of cancers other than neuroblastoma, comprising the detection of methylation of CASP8 gene. The specification does

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not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments have been carefully considered, but are unpersuasive. With regard to the scope enablement for methods of prognosis, the specification is enabling for methods of prognosis of neuroblastoma comprising the detection of a methylation of CASP8 gene, because the specification provides data showing that methylation of CASP8 gene is associated with overexpression of MYCN gene, which is a finding that is associated with a poor prognosis for neuroblastoma. The specification reports that methylation of CASP8 gene has been found in lung cancer, and applicants have provided post-filing date reports of methylation studies in other pediatric cancers. However, these post-filing date reports do not show that methylation of CASP8 gene is associated with disease prognosis. In fact, Harada (provided by applicants in response) points out at page 5898 (2<sup>nd</sup> column) that "There was no relationship between methylation status and other clinicopathological parameters" [*other than age of patient*]. Therefore, the rejection is maintained with respect to rejection of the claims to methods for prognosis of any cancer.

With regard to the enablement of claims to methods of diagnosis of a cancer, applicants' arguments are not persuasive, because neither the specification nor the post-filing date references supplied by applicant show how methylation of CASP8 may be used as a tool for the diagnosis of cancer in general. In all cases, the tested samples from patients, were from patients that already were diagnosed with cancer. The specification and the references supplied by applicant lack retrospective studies to demonstrate that assessment of CASP8 methylation status may be used to diagnose cancer. The specification does provide one possible diagnosis that may be

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incorporated into the claims, and that is that the detection of CASP8 methylation may be used for the diagnosis of high-risk neuroblastoma from low-risk neuroblastoma.

10. The rejection of claims 29 and 58 under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim (Boehringer Mannheim, 1997 Biochemicals Catalog) is maintained for the reasons of record. Claims 29 and 58 are drawn to kits comprising primers for amplification of at least a part of the 5' untranslated region of CASP8 genomic DNA, wherein the primers are used in a methylation polymerase chain reaction (PCR) assay, or for the amplification of regions comprising SEQ ID NO: 1 or comprising SEQ ID NO: 2.

The amendment adding the phrase "CASP8 gene-specific" fails to obviate the rejection. This is because the claims recite that the kits "comprise" oligonucleotide primers, and because the specification fails to define "CASP8 gene-specific".

Claims 29 and 58 read on random hexamer mixtures of Boehringer Mannheim, because the primers are to be used for the amplification of at least a part of the 5' untranslated region or for amplification of sequences that comprise either SEQ ID NO: 1 or SEQ ID NO: 2. Therefore, Boehringer Mannheim teaches kits that are the same as that claimed.

***New Grounds of Rejection:***

*These rejections were necessitated by amendment.*

11. Claims 29, 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 29 and 58 are indefinite because of the phrase "CASP8 gene-specific". The specification contains no definition of this phrase, and also defines CASP8 gene as including allelic genes, nucleotide sequences comprising all or portion of CASP8 genes which are altered by the substitution of different codons, where either a silent change is produced in the coding region or a non-silent change is produced, and also as including CASP8 derivatives. The boundary for CASP8 gene associated sequences is not defined, so that it is not possible to assess when a primer is CASP8 gene-specific or not.

12. Claims 29 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment to claims 29 and 58, adding the phrase "CASP8 gene-specific" introduces new matter into the specification.

The passages cited by applicants as providing support for "CASP8 gene-specific" do not contain this phrase, and do not appear to provide a definition of this phrase. While the specification provides some examples of primer sequences (SEQ ID NO: 29-SEQ ID NO: 34) that fall within the definition of "CASP8 gene-specific", these sequences are not representative of the genus of "CASP8 gene-specific" because the specification provides a broad definition of CASP8 gene and because the specification fails to define a boundary for the CASP8 gene so that one would know when a sequence was specific for CASP8 gene or not. Therefore, the

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specification contains no written description for "CASP8 gene-specific" and this amendment introduces new matter into the specification as originally filed.

### ***Conclusion***

Claims 56, 60, 61, 57 and 62 are allowed. Claims 51, 63, 11, 12, 16, 29, 58 and 59 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.



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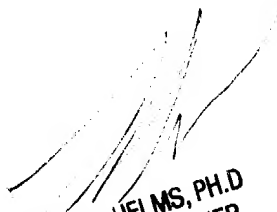
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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran  
Patent Examiner

October 3, 2004



LARRY R. HELMS, PH.D  
PRIMARY EXAMINER